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Dutasteride improves bone mineral density in male patients with lower urinary tract symptoms and prostatic enlargement: a preliminary study.

Wada Naoki, Hashizume Kazumi, Matsumoto Seiji, Kakizaki Hidehiro.

**TITLE PAGE****Dutasteride improves bone mineral density in male patients with lower urinary tract symptoms and prostatic enlargement: a preliminary study**

Naoki Wada, Kazumi Hashizume, Seiji Matsumoto, Hidehiro Kakizaki

Department of Renal and Urologic Surgery, Asahikawa Medical University, Asahikawa, Japan

Corresponding to: Naoki Wada, M.D, Ph.D.

Department of Renal and Urologic Surgery, Asahikawa Medical University

2-1-1-1 Midorigaoka Higashi, Asahikawa, 078-8510, Japan

E-mail : [nwada@asahikawa-med.ac.jp](mailto:nwada@asahikawa-med.ac.jp)

TEL: +81 166 68 2533

FAX: +81 166 68 2539

**Short Running title:** Dutasteride and bone mineral density

**ABSTRACT (250words)**

**INTRODUCTION:** We studied the effect of dutasteride on bone mineral density (BMD) in aging male patients with lower urinary tract symptoms (LUTS) and prostatic enlargement.

**METHODS:** We prospectively studied 17 patients with LUTS and prostatic enlargement. Before and one year after dutasteride (0.5mg daily), we assessed International Prostate Symptom Score (IPSS), prostatic volume (PV), serum prostatic specific antigen (PSA) and testosterone. BMD in the lumbar and femur was measured by DEXA method.

**RESULTS:** Dutasteride significantly reduced PV (from 51  $\pm$ 24 to 34  $\pm$ 17 ml,  $P<0.001$ ) and improved IPSS (from 15.1  $\pm$ 9.8 to 11.7  $\pm$ 10.3,  $P<0.05$ ). Serum PSA was significantly decreased (from 3.2  $\pm$ 2.6 to 1.0  $\pm$ 0.8 ng/ml,  $P<0.001$ ), while serum testosterone **was not changed** significantly. BMD of the lumbar **was not changed** significantly after dutasteride. BMD of the femur was significantly improved (from 0.75  $\pm$ 0.14 to 0.82  $\pm$ 0.16 g/cm<sup>2</sup>,  $P<0.01$ ). In 9 patients whose testosterone was increased after dutasteride, BMD of the lumbar (from 1.18  $\pm$ 0.26 to 1.22  $\pm$ 0.25 g/cm<sup>2</sup>,  $P<0.05$ ) and femur (from 0.76  $\pm$ 0.12 to 0.84  $\pm$ 0.16 g/cm<sup>2</sup>,  $P<0.05$ ) was significantly improved.

**CONCLUSIONS:** Dutasteride has a potential to improve BMD with elevation of serum testosterone in aging male patients with LUTS and prostatic enlargement.

**Key words:** bone mineral density, benign prostatic hyperplasia, dutasteride

**TEXT****INTRODUCTION**

Dutasteride, a dual  $5\alpha$ -reductase inhibitor has been widely used for treatment of patients with lower urinary tract symptoms (LUTS) and prostatic enlargement. This drug inhibits action of  $5\alpha$ -reductase that converts testosterone into dihydrotestosterone (DHT) and reduces prostatic volume (PV) [1]. As a result, DHT production is almost totally inhibited and serum testosterone is elevated to some extent by dutasteride [2].

Testosterone has various important physiological roles in men. However, testosterone is slowly and steadily decreased with age, and the decreased testosterone is closely associated with sexual dysfunction (erectile dysfunction and decreased libido), fatigue, depressed mood, and weakness of muscle and bone [3, 4]. The prevalence of osteoporosis or bone fracture is generally higher in female population than **in** male. However, mortality after bone fracture, especially hip fracture, is reported to be higher in men than in women [5]. Some studies reported osteoporosis itself **could** influence life expectancy regardless of bone fracture [6]. Therefore it is important to prevent bone fracture or osteoporosis in male population.

According to the Japanese surveillance on osteoporosis and bone fracture, the incidence of osteoporosis and bone fracture in male population is gradually increasing from 50's and 70's, respectively [7, 8]. Similarly, the prevalence of LUTS associated with prostatic enlargement is also increasing from 60's [9]. Thus the age of male population with decreased bone density and LUTS is overlapping. There are only a few studies that examined the effect of  $5\alpha$ -reductase inhibition with dutasteride on BMD in male patients with LUTS associated with prostatic enlargement. We prospectively examined the effect of dutasteride on BMD in aging male patients with LUTS to elucidate relationship between changes of testosterone and BMD after

dutasteride treatment.

## METHODS

This was a prospective pilot study. This study was approved by Asahikawa Medical University Ethical Committee and carried out in accordance with the principles of the Declaration of Helsinki.

This study was conducted in consecutive 17 male patients with LUTS and prostatic enlargement who had been taking any alpha adrenergic antagonist for more than 6 months without a previous history of bone fracture. All study patients had been taking no drugs for osteoporosis. Presence of LUTS and prostatic enlargement were defined as more than 8 points of the International Prostate Symptom Score (IPSS) and more than 30 ml of prostatic volume (PV) measured by transabdominal ultrasonography, respectively. IPSS is one of the tools that have been widely used to evaluate symptoms in male patients with LUTS. Generally, the severity of LUTS is defined as mild, moderate and severe if total score of IPSS is 7 or less, 8-19 and 20 or more, respectively [9].

Study patients received 0.5 mg dutasteride once daily, and before and one year after dutasteride, we evaluated IPSS, PV, serum prostatic specific antigen (PSA), testosterone and BMD of the femur and lumbar. Serum testosterone was expressed as total testosterone level. BMD was measured by dual-energy X-ray absorptiometry (DEXA) and evaluated by the actual value and young adult mean value (YAM). According to the Japanese guideline of osteoporosis [10], the bone loss and osteoporosis for people without a history of fragility fracture are diagnosed by 80% of YAM or less and 70% of YAM or less, respectively.

Change of BMD before and after dutasteride was investigated. Data were expressed as mean

plus or minus standard deviation. Pre- and post-treatment data were analyzed with Wilcoxon matched-pairs signed-ranks test or Chi-square test. P values of <0.05 were regarded as statistically significant.

## RESULTS

All patients completed all examinations. The study patients were 64 to 88 years old (mean age 78 years) with PV of 30 to 97 ml (mean 51 ml). The severity of LUTS was moderate in 13 patients (76%), and severe in 4 (24%). Regarding BMD, mean BMD of **the** femur ( $0.75 \pm 0.14$  g/cm<sup>2</sup>) was lower than that of **the** lumbar ( $1.11 \pm 0.25$  g/cm<sup>2</sup>). According to the Japanese guideline of osteoporosis, 2 patients (12%) at **the** lumbar and 5 (29%) at **the** femur were categorized as bone loss, and one patients (6%) at **the** lumbar and 2 (12%) at **the** femur were categorized as osteoporosis. **There was no parameter** that significantly correlated with BMD of **the** lumbar or femur before dutasteride.

One year after dutasteride, IPSS and PV were significantly decreased (see Table). Serum testosterone **was not changed** significantly after dutasteride. BMD of the femur was significantly increased from  $0.75 \pm 0.14$  to  $0.82 \pm 0.16$  g/cm<sup>2</sup> ( $P < 0.01$ , mean 6% increase), while BMD of the lumbar **was not changed** significantly after dutasteride. In 9 patients whose serum testosterone **was** increased after dutasteride treatment, BMD at the lumbar (from  $1.18 \pm 0.26$  to  $1.22 \pm 0.25$  g/cm<sup>2</sup>,  $P < 0.05$ , mean 3% increase) and femur (from  $0.76 \pm 0.12$  to  $0.84 \pm 0.16$  g/cm<sup>2</sup>,  $P < 0.05$ , mean 11% increase) was significantly increased. **In other 8 patients whose serum testosterone was stable or decreased, BMD at both the lumber and femur was not changed significantly.**

## DISCUSSION

**This pilot study demonstrated that one year dutasteride treatment improved BMD in the lumbar and femur in 9 out of 17 male patients with LUTS and prostatic enlargement. In these 9 patients, the improvement of BMD was associated with a significant increase in testosterone. Thus** improvement of BMD **after dutasteride** might depend on elevation of serum testosterone after dutasteride. For aging male population, dutasteride can have a beneficial effect on bone health and LUTS associated with prostatic enlargement.

Previous studies reported the effect of finasteride, the other 5 $\alpha$ -reductase inhibitor, on BMD. However, they focused on adverse effects of DHT inhibition by 5 $\alpha$ -reductase inhibitor [11-13]. They concluded that finasteride did not impair bone health in young or old men. Amory et al. demonstrated that both finasteride and dutasteride did not have a significant impact on BMD [13]. However their subjects were younger men (age 18 to 55 years with a mean age 34) and BMD was normal in all subjects [13]. In contrast, the patients in the present study were much older than those in previous studies and 29% of them were judged as bone loss of **the** femur at baseline.

Dutasteride inhibits DHT production almost totally and elevates serum testosterone to some extent. However, in the present study serum testosterone **was not changed** significantly after dutasteride. Hong et al indicated that the increase in serum testosterone was higher in patients with lower serum testosterone at baseline [2]. Shigehara et al also showed that in patients with >20% increase in serum testosterone level after dutasteride, testosterone at baseline was significantly lower than that of patients with <20% increase or decrease of serum testosterone [14]. In the present study, serum testosterone was increased after dutasteride in 9 out of 17 patients (53%). When all 17 patients were included for analysis, only BMD of the femur but not

of the lumbar was significantly increased after dutasteride. However, in the 9 patients whose serum testosterone was increased after dutasteride, BMD of the both femur and lumbar was significantly increased. **Furthermore, in 8 patients whose testosterone was stable or decreased, BMD of the both femur and lumbar was not changed significantly.** These results indicate that the increase of serum testosterone might influence the elevation of BMD.

The relationship between testosterone and BMD has been inconsistent and inconclusive according to previous studies. Sex hormones including estrogens affect proliferation, differentiation and apoptosis of **osteoblasts, osteoclasts and osteocytes** to varying degrees. However, it is still unclear what specific role for bone health a single hormone has [15]. We did not measure estrogen level including estradiol in the present study. Some studies investigated the relationship between BMD and estrogen. Positive association was found between estradiol and BMD, while higher estrogen in young men was associated with more bone gain and higher estrogen in elderly men was associated with less bone loss [15, 16]. BMD was inversely correlated to testosterone level in middle aged men [15, 17]. Clinical relationship between testosterone, estrogen and BMD seems to be complicated and controversial.

Many clinical studies have supported that testosterone replacement therapy can increase BMD. Based on a meta-analysis about the effect of testosterone use on men's bone health, testosterone use significantly increased the lumbar and femur BMD by 4% [18]. The change of BMD of the lumbar and femur in the present study is not inferior to the meta-analysis data. Shigehara et al also investigated the effect of dutasteride on general health including BMD in hypogonadal men [14]. **They showed positive effects of dutasteride on urinary function and improvement of BMD with simultaneous increase of serum testosterone.** Considering adverse effects of extrinsic testosterone replacement therapy, intrinsic increase of testosterone by

dutasteride might be a safe option for patients with lower testosterone level.

**Because the present study was very small, preliminary and no placebo-controlled study, we need a large-scaled and placebo-controlled study to explore the effect of dutasteride and sex hormones on bone health in men.** Potential roles of other sex hormones including estrogen should also be examined. Because the present study included the patients with normal BMD, it might be better that future study should include only patients with bone loss or osteoporosis to elucidate a more profound effect of dutasteride on BMD.

**In conclusion, dutasteride has a potential to improve BMD with elevation of serum testosterone in aging male patients with LUTS and prostatic enlargement.**

#### **Conflicts of Interest**

All authors declare no conflict of interest.

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**Change of each parameter before and after dutasteride**

	Baseline	1 yr after dutasteride	P value	
PV (ml)	51 ± 24	34 ± 17	<0.001	
IPSS	15.1 ± 9.8	11.7 ± 10.3	<0.05	
	Mild	0	8 (47%)	
	Moderate	13 (76%)	5 (28%)	
	Severe	4 (24%)	4 (25%)	
			<0.01†	
PSA (ng/ml)	3.2 ± 2.6	1.0 ± 0.8	<0.001	
Testosterone (ng/dl)	434 ± 132	462 ± 163	0.23	
BMD (g/cm <sup>2</sup> )				
	Lumber	1.11 ± 0.25	1.13 ± 0.25	0.12
	Bone loss	2 (12%)	3 (18%)	
	Osteoporosis	1 (6%)	1 (6%)	0.89†
	Femur	0.75 ± 0.14	0.82 ± 0.16	<0.01
	Bone loss	5 (29%)	3 (18%)	
	Osteoporosis	2 (12%)	2 (12%)	0.71†
<b>In 9 patients whose testosterone was increased after dutasteride</b>				
Testosterone (ng/dl)	416 ± 134	506 ± 165	<0.001	
BMD (g/cm <sup>2</sup> )				
	Lumber	1.18 ± 0.26	1.22 ± 0.25	<0.05
	Femur	0.76 ± 0.12	0.84 ± 0.16	<0.05
<b>In 8 patients whose testosterone was stable or decreased after dutasteride</b>				
Testosterone (ng/dl)	455 ± 128	404 ± 141	<0.001	
BMD (g/cm <sup>2</sup> )				
	Lumber	1.03 ± 0.22	1.02 ± 0.21	0.13
	Femur	0.73 ± 0.16	0.80 ± 0.17	0.10

Express as mean ± SD

Using Wilcoxon matched-pairs signed-ranks test except for † using Chi-square test.